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ABOUT COVER

Editorial board member of *World Journal of Hepatology*, Dr. Alberto Ferrarese is a Gastroenterologist devoted to the field of hepatology. He obtained his MD degree at Padua University Hospital, Italy, where his ongoing career research has focused mainly on decompensated cirrhosis and liver transplantation. His main research interests are complications of cirrhosis, bacterial infection in cirrhosis, organ allocation in liver transplantation, and adherence and quality of life after liver transplantation. He has authored 40 articles published in international peer-reviewed journals and he serves as a reviewer for several international journals in the field of hepatology. (L-Editor: Filipodia)

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Glucagon-like peptide-1 receptor agonists in non-alcoholic fatty liver disease: An update

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the predominant cause of chronic liver disease worldwide. NAFLD progresses in some cases to non-alcoholic steatohepatitis (NASH), which is characterized, in addition to liver fat deposition, by hepatocyte ballooning, inflammation and liver fibrosis, and in some cases may lead to hepatocellular carcinoma. NAFLD prevalence increases along with the rising incidence of type 2 diabetes mellitus (T2DM). Currently, lifestyle interventions and weight loss are used as the major therapeutic strategy in the vast majority of patients with NAFLD. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are used in the management of T2DM and do not have major side effects like hypoglycemia. In patients with NAFLD, the GLP-1 receptor production is down-regulated. Recently, several animal and human studies have emphasized the role of GLP-1RAs in ameliorating liver fat accumulation, alleviating the inflammatory environment and preventing NAFLD progression to NASH. In this review, we summarize the updated literature data on the beneficial effects of GLP-1RAs in NAFLD/NASH. Finally, as GLP-1RAs seem to be an attractive therapeutic option for T2DM patients with concomitant NAFLD, we discuss whether GLP-1RAs should represent the first line pharmacotherapy for these patients.

Key words: Glucagon-like peptide-1 receptor agonists; Non-alcoholic fatty liver disease; Type 2 diabetes mellitus; Clinical studies; Fatty liver; Animal studies

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Core tip: The strong relationship between non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus points to a need to evaluate the therapeutic potential of antidiabetic drugs in patients with NAFLD. Accordingly, glucagon-like peptide-1 receptor agonists, which are well-tolerated antidiabetic agents with no risk of hypoglycemia, seem to be a very appealing therapeutic option for type 2 diabetes mellitus patients with NAFLD. Herein, based on data from animal studies and clinical trials, we discuss the beneficial impact of glucagon-like peptide-1 receptor agonists on NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases, affecting approximately one third of the population globally^[1]. It includes a wide spectrum of clinical presentations, from isolated fat accumulation in the liver to inflammation and fibrosis [*i.e.*, non-alcoholic steatohepatitis (NASH)], cirrhosis and hepatocellular carcinoma^[2]. NAFLD is inextricably linked to major comorbidities of the metabolic syndrome, including obesity, insulin resistance, type 2 diabetes mellitus (T2DM) and dyslipidemia^[3]. In addition, various metabolism disorders, including thyroid dysfunction, are associated with the occurrence of NAFLD. Of note, thyroid hormones are of cardinal importance in regulating fat deposition and insulin resistance as well as lipid and carbohydrate metabolism, thereby contributing to NAFLD/NASH modification^[4,5].

Hypothyroidism has been suggested as an independent risk factor for NAFLD/NASH development in both adult and children/adolescent population. Moreover, the inconsistent findings on current literature regarding the association between NAFLD and free thyroid hormones (free triiodothyronine and free thyroxine) may indicate a key role for thyroid-stimulating hormone in NAFLD onset and progression, independently of free triiodothyronine and free thyroxine^[4]. The increasing prevalence of NAFLD in combination with its severe complications underlines the need for effective and safe treatments. Presently, diet and lifestyle changes are the main treatment options for NAFLD, whereas vitamin E and pioglitazone have limited application, mostly in non-diabetic patients^[6].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are used for the treatment of T2DM^[7]. This class includes exenatide, lixisenatide, liraglutide, albiglutide, semaglutide and dulaglutide^[8]. GLP-1RAs are divided into short- and long-acting^[8]. The former include exenatide and lixisenatide, whereas the latter include liraglutide, albiglutide, dulaglutide, semaglutide and once weekly exenatide^[8]. GLP-1 receptors are expressed mainly in the pancreas but are also present in the brain, adipose tissue, muscles, heart, kidney, lung, stomach and hepatocytes^[7,9,10]. Their primary actions are the stimulation of insulin secretion and the reduction of glucagon secretion^[7]. In patients with T2DM, they reduce hemoglobin A1c (HbA_{1c}) levels by approximately 1.5% without the risk of hypoglycemia^[8]. Their main side effects are nausea and vomiting^[8]. Interestingly, the production of GLP-1 is reduced in patients with NAFLD^[11].

Accumulating data suggest that GLP-1RAs improve liver histology in patients with NAFLD. In the present review, we discuss the role of these agents in the management of NAFLD.

LITERATURE RESEARCH

We systematically reviewed the literature in the PubMed database up to December 2019. The following search terms were used: "(GLP-1 receptor agonists OR glucagon-like peptide-1 agonists OR glucagon-like peptide-1 analogues OR GLP-1 analogues OR liraglutide OR exenatide OR semaglutide OR dulaglutide OR lixisenatide OR

albiglutide) AND (NASH OR NAFLD OR non-alcoholic fatty liver disease OR fatty liver disease OR non-alcoholic steatohepatitis).

EXENATIDE

Effects of exenatide in animal models of NAFLD

Several studies reported beneficial effects of exenatide in animal models of NAFLD, and a variety of mechanisms appear to underpin these effects. First, exenatide appears to reduce intrahepatic oxidative stress. Indeed, in rats, administration of exendin-4 resulted in an increase in glutathione levels, which in turn reduced oxidative stress^[12]. A reduction of the hepatic expression of receptors for advanced glycation end-products also appears to contribute to the antioxidant effects of exenatide^[13].

An improvement in insulin resistance also may play a role in the improvement of hepatic steatosis during exenatide treatment. In rats, administration of exendin-4 resulted in an increase in cystathionine beta synthase, which resulted in a reduction in insulin resistance^[12]. Treatment with exendin-4 also results in an increase of adiponectin levels, which again improves insulin sensitivity^[14,15]. In contrast, levels of visfatin, which appears to play a role in insulin resistance, were reduced after treatment with exenatide^[15]. Exenatide also improves insulin sensitivity by increasing peroxisome proliferator-activated receptor (PPAR)- γ activity^[16].

Exenatide exerts anti-inflammatory effects, which contribute to the improvement in hepatic histology in NAFLD. Accordingly, exenatide was shown to inhibit the NLRP3 inflammasome by enhancing the autophagy/mitophagy pathway^[17]. In another study in mice, administration of exendin-4 for 4 wk reduced inflammation both in the liver and in the vascular wall as shown by a decreased accumulation of monocytes and macrophages and a reduced recruitment of oxidized LDL, which correlated with reduced formation of foam cells^[18]. Kawaguchi *et al.*^[19] reported that mice treated with exendin-4 had a lower NAFLD activity score compared with mice that received saline^[19]. This beneficial effect was mediated by an inhibition of the action of Δ -5-desaturase, which resulted in a reduction of pro-inflammatory eicosanoids and an increase in dihomo- γ -linolenic acid and anti-inflammatory eicosanoids^[19].

Another important mechanism implicated in the reduction of hepatic fat accumulation during exenatide treatment is the amelioration of hepatic lipid metabolism. Exenatide was shown to suppress hepatic very-low density lipoprotein (VLDL) production, resulting in improvement of hepatic steatosis^[20]. Mice treated with exendin-4 showed an increased expression of acyl-CoA oxidase and medium chain acyl-coenzyme A dehydrogenase, which are both related to β -oxidation^[9]. In addition, the expression of several enzymes participating in hepatic lipid metabolism, including sirtuin-1, phospho-5' adenosine monophosphate-activated protein kinase, phospho-Foxo1 and glucose transporter 2, was also up-regulated during exendin-4 treatment^[9]. On the other hand, the levels of modulators of hepatic lipogenesis such as sterol regulatory element-binding protein-1c (SREBP-1c) and stearoyl CoA desaturase-1 mRNA were decreased^[9]. Exenatide-induced up-regulation of sirtuin also increases fibroblast growth factor-1 activity, which is another important regulator of hepatic lipid metabolism^[21]. During treatment with exenatide, enzymes related to hepatic lipogenesis, including ACC, stearoyl CoA desaturase-1 and SREBP-1c are down-regulated whereas enzymes participating in β -oxidation, including PPAR α and fatty acyl-CoA oxidase, are up-regulated^[14].

Yamamoto *et al.*^[22] randomly assigned male db/db non-obese NASH mice to methionine-choline sufficient diet or methionine-choline deficient diet (MCD), a well-established inducer of hepatic steatosis and inflammation, plus exendin-4 (20 μ g/kg per day intraperitoneally) or MCD plus saline for 4 or 8 wk^[22]. Exendin-4 administration significantly ameliorated both the MCD-induced oil red O-positive area, an index of hepatic fat deposition, and the liver triglyceride content in the MCD plus exendin-4 group compared to the saline group at 4 and 8 wk through suppression of FATP4, which plays a role in hepatic free fatty acid uptake^[22]. In addition, exendin-4 administration led to significant decreased mRNA expression of SREBP-1c, a gene responsible for free fatty acid production in MCD-fed mice at 4 and 8 wk, along with markedly reduced serum alanine transaminase (ALT) levels at 8, but not at 4 wk, in the same group^[22]. Of note, exendin-4 therapy attenuated the increased, by MCD, hepatic mRNA expression levels of inflammation-related genes such as tumor necrosis factor- α , monocyte chemoattractant protein-1 and cc-chemokine receptor 2 and also decreased insulin levels and homeostasis model assessment of insulin resistance^[22].

In rabbits, treatment with exenatide decreased the expression of fat mass and

obesity-associated gene (*FTO*), which is associated with both lipogenesis and oxidative stress^[23]. In another study, treatment with exenatide improved histological features of NAFLD through enhancing the action of PPAR α , which is another key regulator of fatty acid β -oxidation^[16]. In mice, exendin-4 reduced VLDL-triglycerides and VLDL-ApoB, inhibited the expression of *Srebp-1c*, *Fasn* and *Dgat1*, which participate in hepatic lipogenesis, and down-regulated the genes *Acox1* and *Cpt1a*, which play a role in fatty acid oxidation^[20].

Endoplasmic reticulum (ER) stress appears to play an important role in the pathogenesis of hepatic steatosis, and exenatide was shown to alleviate ER stress by enhancing the sirtuin 1/heat shock factor 1/heat shock protein pathway^[24,25]. Treatment of mice with exenatide was also shown to improve mitochondrial lipid metabolism, which in turn resulted in decreased steatosis^[26]. Exenatide also activates the phosphoinositide 3-kinase/Akt pathway, which might improve liver histology in NAFLD through the regeneration of hepatocytes^[23].

In addition to these effects of exenatide on the liver, an enhancement of lipid catabolism in the adipose tissue during treatment with this agent also appears to ameliorate hepatic steatosis by decreasing free fatty acid influx into the liver^[27]. Interestingly, it has been recently reported that co-agonists of GLP-1 and glucagon receptor ameliorate hepatic steatosis and inflammation more than GLP-1 agonists alone^[28]. The concomitant administration of exendin-4 and glucokinase activator in mice also resulted in a reduction of liver steatosis, liver weight, intrahepatic triglyceride levels and serum ALT levels^[29].

Effects of exenatide in clinical studies of NAFLD

It is of interest whether data from animal studies can be translated into humans, in order to clarify the beneficial impact of GLP-1RAs on human NAFLD (Table 1). In particular, in a study by Gastaldelli *et al.*^[30], 15 males with newly diagnosed T2DM or impaired glucose tolerance were randomized to receive exenatide or placebo, each therapy on two sessions with random order, 30 min before the performance of an oral glucose tolerance test (OGTT)^[30]. Adipose tissue glucose uptake, hepatic glucose uptake, hepatic glucose production and oral glucose absorption were assessed by positron emission tomography scan^[30]. Exenatide, compared to placebo, markedly reduced oral glucose absorption and hepatic glucose production, resulting in minimal change in glucose serum concentration during the 2-h OGTT. In addition, treatment with exenatide reduced hepatic and adipose tissue insulin resistance and increased hepatic glucose uptake compared with placebo resulting in postprandial euglycemia^[30]. The aforementioned findings were observed despite a decrease in insulin levels by exenatide compared with placebo^[30].

In addition, a prospective randomized trial was conducted in order to clarify the effect of exenatide on ectopic fat accumulation^[31]. Forty four obese patients with inadequately controlled T2DM were randomized to receive either exenatide (5 μ g twice daily for 4 wk, followed by 10 μ g twice daily for 22 wk) or reference antidiabetic treatment according to French guidelines^[31]. Patients' hepatic, myocardial and pancreatic triglyceride content as well as epicardial adipose tissue were assessed by magnetic resonance imaging and magnetic resonance spectrometry (MRS) at baseline and after 26 wk of treatment^[31]. In the exenatide group compared with the reference group, anthropometric parameters such as body weight, waist, thigh and hip circumference and laboratory values, such as fasting plasma insulin, total cholesterol and palmitoleic acid plasma levels, were decreased^[31]. Moreover, a significant reduction in epicardial adipose tissue mass and liver fat content was observed in the exenatide compared with the reference group, and both correlated with weight loss^[31].

In an open-label, parallel-group, uncontrolled, 6-mo study, the effect of exenatide on hepatic fat accumulation and liver enzymes was evaluated^[32]. One hundred and twenty five patients with T2DM were divided into two groups: The first group received exenatide (10 μ g twice daily) alone or in combination with other oral antidiabetic drugs while the second group received oral antidiabetic drugs without exenatide for 6 mos^[32]. At the end of follow-up, group 1, compared with group 2, had reduced values of body mass index, waist circumference, alkaline phosphatase, ALT and intrahepatic fat accumulation (calculated by the fatty liver index)^[32].

Of note, in a small prospective study, 25 obese patients with NAFLD and inadequately-controlled T2DM despite treatment with metformin and sulphonylureas or dipeptidyl-peptidase-IV inhibitors, received GLP-1RA (exenatide in 19 patients and liraglutide in six patients) for a period of 6 mo^[33]. At the end of the study, GLP-1RA treatment resulted in a 7%-11% reduction in abdominal visceral adipose tissue and subcutaneous adipose tissue, while HbA_{1c}, ALT and γ -glutamyl-transferase (γ GT) levels improved along with a marked increase in serum adiponectin levels^[33]. In

Table 1 Characteristics and outcomes of clinical studies that evaluated the effects of exenatide, lixisenatide and dulaglutide on non-alcoholic fatty liver disease

Ref.	Type of study, country	Number of patients	Treatment	Effects on NAFLD
Gastaldelli <i>et al</i> ^[30] , 2016	Randomized double-blind <i>vs</i> placebo/Pisa, Italy	15	Exenatide 5 µg <i>vs</i> placebo 30 min before a 75-g OGTT	Exenatide significantly ameliorated oral glucose absorption, hepatic glucose production, hepatic and adipose tissue insulin resistance, reduced insulin levels and increased hepatic glucose uptake
Dutour <i>et al</i> ^[31] , 2016	Prospective randomized trial, France	44	Exenatide 5 µg twice daily for 4 wk, followed by 10 µg twice daily for additional 22 wk <i>vs</i> reference antidiabetic treatment according to French guidelines	Exenatide markedly reduced body weight, waist, thigh, hip circumference, fasting plasma insulin, total cholesterol and palmitoleic acid plasma levels
Blaslov <i>et al</i> ^[32] , 2014	Open label parallel-group, uncontrolled study, Croatia	125	Exenatide (10 µg twice daily) on its own or in combination with other oral antidiabetic drugs <i>vs</i> other oral antidiabetic drugs without exenatide for 6 mo	Exenatide remarkably attenuated body mass index, waist circumference, ALP, ALT, intrahepatic fat accumulation assessed by fatty liver index
Cuthbertson <i>et al</i> ^[33] , 2012	Prospective study, United Kingdom	25 [exenatide (<i>n</i> = 19), liraglutide (<i>n</i> = 6)]	Exenatide 5 µg twice daily titrated to 10 µg twice daily after one month; liraglutide 0.6 mg once daily, titrated to 1.2 mg once daily for 6 mo	GLP-1RA reduced, compared to baseline, abdominal visceral and subcutaneous adipose tissue, HbA1c, ALT, γ-GT and intrahepatic lipid content and increased adiponectin serum levels
Fan <i>et al</i> ^[34] , 2013	Randomized clinical trial, China	117	Exenatide (5 µg for four weeks followed by 10 µg for additional 8 wk, two times daily) <i>vs</i> metformin (0.5-2 g/d)	Exenatide decreased body weight, waist-to-hip ratio, ALT, AST, AST/ALT ratio, γ-GT, 2-h postprandial glucose serum levels, CRP and increased adiponectin serum levels
Savvidou <i>et al</i> ^[35] , 2016	Open label, randomized controlled intervention trial, Greece	120	Exenatide 5 µg twice daily for 4 wk and 10 µg twice daily as supplementation on glargine insulin <i>vs</i> intense self-regulated insulin therapy for 6 mo	Both therapies significantly increased adiponectin serum levels compared to baseline, but no significant change between the groups; Exenatide, compared to insulin group, reduced more robustly body weight but not HbA1c
Shao <i>et al</i> ^[37] , 2014	Randomized controlled trial, China	60	Exenatide 5 µg twice daily, followed by 10 µg twice daily for additional 8 wk plus insulin glargine <i>vs</i> intensive insulin therapy with insulin glargine and insulin as part for a time period of 12 wk	Body weight, waist circumference, ALT, AST, γ-GT were markedly reduced in exenatide compared to insulin group, while levels of fasting blood glucose, postprandial blood glucose, HbA1c, triglyceride and total bilirubin were significantly reduced at both groups at 12 wk, compared to baseline
Bi <i>et al</i> ^[38] , 2014	Randomized controlled trial, China	33	Exenatide 5 µg twice daily for 4 wk, followed by maximum 10 µg twice daily for 20 wk <i>vs</i> insulin <i>vs</i> pioglitazone 30 mg daily, titrated to 45 mg at fourth week, 6 mo study	Exenatide reduced, compared to baseline, intrahepatic fat, visceral and subcutaneous fat volumes, body weight, waist circumference, serum triglycerides, HbA1c, TNF-α
Sathyanarayana <i>et al</i> ^[39] , 2011	Randomized controlled study, United States	21	Exenatide 10 µg twice daily plus pioglitazone 45 mg/d <i>vs</i> pioglitazone 45 mg/d for 12 mo	Combination pharmacotherapy with exenatide, compared to pioglitazone, significantly decreased serum ALT and triglyceride levels as well as intrahepatic fat content and increased adiponectin plasma levels
Gluud <i>et al</i> ^[41] , 2014	Review, Denmark	15 studies included in this meta-analysis	12 randomized clinical trials on lixisenatide <i>vs</i> placebo and 3 randomized clinical trials on lixisenatide <i>vs</i> liraglutide, exenatide or sitagliptin	Lixisenatide markedly increased the proportion of overweight or obese patients with T2DM who achieved ALT levels normalization
Seko <i>et al</i> ^[42] , 2017	Retrospective study, Japan	15	Dulaglutide 0.75 mg once weekly for 12 wk	Dulaglutide, compared to baseline, reduced body weight, ALT, AST, HbA1c and liver stiffness
Ghosh <i>et al</i> ^[43] , 2019	Retrospective study, India	85 T2DM overweight patients	Dulaglutide 1.5 mg once weekly for 20 wk	Dulaglutide led to significant reductions in HbA1c, body weight, ALT and AST levels
Cusi <i>et al</i> ^[44] , 2018	Post hoc analysis, multicenter	4 randomized, placebo-controlled trials with 1499 T2DM patients	Dulaglutide 1.5 mg once weekly for 6 mo	Dulaglutide, compared to placebo, significantly decreased ALT, AST, γ-GT, particularly in patients with elevated transaminase levels at the onset of the study

NAFLD: Non-alcoholic fatty liver disease; OGTT: Oral glucose tolerance test; ALP: Alkaline phosphatase; ALT: Alanine transaminase; GLP-1RA: Glucagon-like peptide-1 receptor agonists; AST: Aspartate aminotransferase; CRP: C-reactive protein; T2DM: Type 2 diabetes mellitus; γ -GT: γ -glutamyl-transferase.

parallel, intrahepatic lipid content, evaluated by MRS, was reduced by 42% at 24 wk compared with baseline, a change that correlated with HbA_{1c} reduction during the same time period^[33].

In a larger study including 117 patients with T2DM and NAFLD, Fan *et al*^[34] assessed the impact of exenatide on anthropometric and laboratory values. The patients were randomly assigned to receive either exenatide (5 μ g for 4 wk followed by 10 μ g for 8 wk, two times daily) or metformin (0.5-2 g/d)^[34]. At the end of follow-up (12 wk), in the exenatide group, compared with the metformin group, body weight, waist-to-hip ratio, ALT, aspartate aminotransferase (AST), AST to ALT ratio, γ GT and 2-h postprandial glucose serum levels were markedly reduced^[34]. Interestingly, high-sensitivity C-reactive protein (hsCRP) levels, a marker of subclinical inflammation, were improved and adiponectin serum levels were significantly increased in the exenatide group compared to the metformin group, and these changes might have played a role in the reduction in transaminase levels^[34].

Indeed, adiponectin appears to exert a hepato-protective effect in patients with NAFLD^[35]. Exendin-4 also appears to protect hepatocytes from steatosis through autophagy and reduction of apoptosis associated with ER stress^[36]. The latter is associated with intrahepatic fat accumulation, but autophagy has a protective role on cell survival^[36]. Accumulation of fatty acids is related to ER stress, cell death, apoptosis and elevated caspase-3 levels, while administration of exendin-4 reduces caspase-3 levels^[36]. In another study, patients with NAFLD who were treated with exenatide had lower levels of AST, ALT and γ GT, compared with patients treated with insulin^[37]. Exenatide also induced a reduction of intrahepatic fat, visceral fat and subcutaneous fat^[38]. In a small study in 21 patients, the combination of exenatide and pioglitazone resulted in a reduction in intrahepatic fat content, serum ALT and triglyceride levels and in an increase in plasma adiponectin levels^[39].

LIXISENATIDE AND DULAGLUTIDE

There are limited data regarding the effects of lixisenatide and dulaglutide on NAFLD (Table 1). In a study in conscious dogs, lixisenatide did not affect hepatic glucose uptake^[40]. In a meta-analysis of 12 randomized controlled trials, lixisenatide increased the proportion of obese or overweight patients with T2DM who achieved normalization of ALT levels^[41]. On the other hand, the administration of dulaglutide for 12 wk at a dose of 0.75 mg once weekly in patients with NAFLD reduced HbA_{1c} levels, body weight, transaminases and liver stiffness^[42]. In another study in 85 overweight patients with inadequately controlled T2DM conducted in India, treatment

with dulaglutide 1.5 mg once weekly for 20 wk resulted in significant reductions in HbA_{1c}, body weight, ALT and AST levels^[43]. Also, in a post hoc analysis of four randomized, placebo-controlled trials in patients with T2DM ($n = 1499$), dulaglutide decreased transaminase and γ GT levels compared with placebo, particularly in patients with elevated transaminase levels at baseline^[44].

LIRAGLUTIDE

In a prospective study, liraglutide was administered for 6 mo in 19 women with polycystic ovary syndrome and controls^[45]. Serum procollagen type 3 amino-terminal peptide levels, a marker of hepatic fibrosis, decreased in patients with polycystic ovary syndrome but not in controls^[45]. In another study in 26 patients with glucose intolerance and biopsy-proven NASH, treatment with liraglutide for 24 wk reduced ALT levels^[46]. Ten patients were treated with liraglutide for 96 wk, and liver biopsy at the end of treatment showed an improvement in liver histology in six of them^[46]. In a retrospective study that included 46 patients, the liver to kidney attenuation ratio in computed tomography (an index of hepatic steatosis) increased after treatment with liraglutide 0.9 mg/d for 6 mo^[47]. Another retrospective analysis of 82 patients with NAFLD who were treated with sitagliptin, liraglutide or pioglitazone revealed that patients who received sitagliptin showed a decrease in ALT activity whereas the AST to platelet count ratio index (APRI score), a marker of liver fibrosis, did not change^[48]. In contrast, patients treated with liraglutide or pioglitazone experienced a decrease in both ALT activity and APRI^[48]. In a subgroup analysis of the Liraglutide Effect and Action in Diabetes-2 trial, 103 patients were treated with liraglutide 0.6, 1.2 and 1.8 mg/d, 37 patients received glimepiride and 20 were given placebo for 26 wk^[49]. Liver to spleen attenuation ratio increased in patients treated with liraglutide 1.8 mg but did not change in those treated with lower doses of liraglutide or with glimepiride^[49]. ALT activity showed comparable decreases with both agents^[49]. In a more recent study, 30 non-diabetic patients with abdominal obesity and NAFLD were managed with liraglutide or with lifestyle modification^[50]. Liraglutide was effective in decreasing weight, hepatic steatosis and hepatocellular apoptosis, but benefits were not sustained after discontinuation of treatment, in contrast with lifestyle modification^[50].

In another study, 87 patients with T2DM and NAFLD were randomized to receive liraglutide, metformin or gliclazide for 24 wk^[51]. Gliclazide resulted in smaller improvement in liver function and less reduction in intrahepatic fat content, HbA_{1c} levels and body weight compared with liraglutide and metformin^[51]. Slightly greater improvements were achieved with liraglutide than with metformin^[51]. In a single-center, randomized, open-label study in 19 patients with T2DM, liraglutide reduced visceral fat at 24 wk^[52]. Urinary albumin-to-creatinine ratio and hsCRP levels were also significantly reduced by liraglutide at 12 and 24 wk^[52]. HbA_{1c} levels, body weight and hepatic fat also decreased in patients treated with liraglutide^[52]. In a prospective trial in 68 patients with uncontrolled T2DM, treatment with liraglutide for 6 mo was associated with a decrease in body weight and HbA_{1c} and a reduction in liver fat content^[53].

A multicenter, double-blind, randomized, placebo-controlled, phase 2 trial was conducted in four United Kingdom medical centers to compare liraglutide with placebo in overweight patients who showed clinical evidence of NASH^[54]. Nine (39%) of 23 patients who received liraglutide and underwent end-of-treatment liver biopsy had resolution of definite NASH compared with two (9%) of 22 patients in the placebo group^[54]. In another study in patients with T2DM, treatment with liraglutide or sitagliptin for 12 wk did not reduce hepatic steatosis, which was estimated using MRS^[55]. In a study in China, which enrolled 835 patients with T2DM, liraglutide improved blood glucose levels, lipid levels and liver function^[56]. In a similar study, which compared treatment of T2DM with liraglutide or metformin, liraglutide was more effective in alleviating liver inflammation and improving liver function^[57]. Finally, in a prospective study ($n = 25$), treatment with either exenatide or liraglutide for 6 mo decreased ALT activity and hepatic fat content (evaluated with MRS)^[53] (Table 2).

SEMAGLUTIDE

Recently, Newsome *et al.*^[58] evaluated the effects of semaglutide on liver biochemistry (ALT) and hsCRP levels in patients at risk for NAFLD. The authors analyzed data

Table 2 Characteristics and outcomes of clinical studies that evaluated the effects of liraglutide and semaglutide on non-alcoholic fatty liver disease

Ref.	Type of study; country	Number of patients	Treatment	Effects on NAFLD
Kahal <i>et al</i> ^[45] , 2014	Prospective; United Kingdom	36	Liraglutide 0.9 mg/d for 6 mo	Serum procollagen type 3 amino-terminal peptide levels, a marker of hepatic fibrosis, decreased in women with PCOS
Eguchi <i>et al</i> ^[46] , 2014	Prospective; Japan	26	Liraglutide 0.9 mg/d for 24-96 wk	ALT activity decreased. NASH decreased in 6/10 patients who underwent repeat biopsy at 96 wk
Suzuki <i>et al</i> ^[47] , 2013	Retrospective; Japan	46	Liraglutide 0.9 mg/d for 6 mo	Liver to kidney attenuation ratio in CT (an index of hepatic steatosis) increased
Ohki <i>et al</i> ^[48] , 2012	Retrospective; Japan	82	Liraglutide 0.9 mg/d for 340 d or sitagliptin 50-100 mg/d for 250 d or pioglitazone 15 mg/d for 1200 d	ALT activity was reduced with all agents. Liraglutide and pioglitazone but not sitagliptin reduced the APRI score
Jendle <i>et al</i> ^[49] , 2009	Randomized controlled; multicenter	160	Liraglutide 0.6, 1.2 or 1.8 mg/d or glimepiride 4 mg/d or placebo for 26 wk	Liver to spleen attenuation ratio in CT (a marker of hepatic steatosis) increased in patients treated with liraglutide 1.8 mg/d and did not change in those treated with lower doses of liraglutide or glimepiride. ALT activity showed comparable decreases with both agents
Khoo <i>et al</i> ^[50] , 2009	Randomized controlled; Singapore	30	Liraglutide 3 mg/d for 16 wk or lifestyle modification	Liraglutide was effective for decreasing weight, hepatic steatosis and hepatocellular apoptosis, but benefits were not sustained after discontinuation, in contrast with lifestyle modification
Feng <i>et al</i> ^[51] , 2017	Randomized controlled; China	87	Liraglutide, metformin, or gliclazide for 24 wk	Liraglutide has better results in improving liver function, reductions in intrahepatic fat content and HbA1c level, and weight loss than metformin and gliclazide
Bouchi <i>et al</i> ^[52] , 2017	Randomized controlled; Japan	19	Liraglutide 0.9 mg/d plus insulin or insulin alone for 14 wk	Liraglutide reduces visceral fat, hepatic fat accumulation, albuminuria and micro-inflammation and improves QOL
Petit <i>et al</i> ^[53] , 2017	Prospective; France	68	Liraglutide 1.2 mg/d for 6 mo	Liraglutide significantly reduced liver fat content
Armstrong <i>et al</i> ^[54] , 2016	Double-blind, randomized, controlled; multicenter United Kingdom	52	Liraglutide 1.8 mg/d or placebo for 48 wk	Liraglutide led to histological resolution of NASH
Smits <i>et al</i> ^[55] , 2016	Randomized placebo-controlled; Holland	52	Liraglutide 1.8 mg/d, sitagliptin 100 mg/d or placebo	Liraglutide or sitagliptin treatment does not reduce hepatic steatosis or fibrosis
Zhang <i>et al</i> ^[56] , 2016	Randomized controlled; China	835	Liraglutide 1.2 mg/d or metformin 500 mg/3 times per day	Liraglutide improves the blood glucose and lipid levels as well as liver function
Tian <i>et al</i> ^[57] , 2018	Randomized controlled; China	127	Liraglutide 0.6-1.2 mg/d or metformin 1000-1500 mg/d for 12 wk	Liraglutide decreases ALT levels and is more effective than metformin at alleviating liver inflammation and improving liver function
Cuthbertson <i>et al</i> ^[33] , 2012	Prospective; United Kingdom	25	Exenatide 10 mg twice daily or liraglutide 1.2 mg/d	Both liraglutide and exenatide reduce body weight, HbA1c and intrahepatic lipid accumulation
Newsome <i>et al</i> ^[58] , 2019	Retrospective (data from 2 trials); United Kingdom	957 (trial 1) and 3297 (trial 2)	Semaglutide 0.05, 0.1, 0.2, 0.3 or 0.4 mg/d for 52 wk (trial 1) and semaglutide 0.5 or 1.0 mg/wk for 104 wk (trial 2)	Semaglutide significantly reduced ALT and hsCRP in clinical trials in subjects with obesity and/or type 2 diabetes

PCOS: Polycystic ovary syndrome; NAFLD: Non-alcoholic fatty liver disease; ALT: Alanine transaminase; hsCRP: High-sensitivity C-reactive protein; NASH: Non-alcoholic steatohepatitis; CT: Computed tomography; APRI: AST to platelet count ratio index.

from two randomized, double-blind, multinational, placebo-controlled trials: A) A 104-wk cardiovascular outcomes trial, in which semaglutide 0.5 or 1.0 mg was given once weekly subcutaneously in T2DM patients with HbA_{1c} levels $\geq 7\%$ (SUSTAIN-6 trial) and B) A 52-wk weight management trial, in which semaglutide 0.05-0.4 mg was given daily subcutaneously in obese patients without T2DM^[58]. Among patients ($n = 499$, 52%) with abnormal ALT levels (men > 30 IU/L, women > 19 IU/L) at baseline, ALT reductions were observed in 6%-21% of patients at doses ≥ 0.2 mg/d ($P < 0.05$ *vs* placebo) in the weight management trial. Similarly, hsCRP reductions were recorded in 25%-43% of patients receiving semaglutide 0.2 and 0.4 mg/d ($P < 0.05$ *vs* placebo)^[58]. Among those who had abnormal ALT levels and received semaglutide 0.4 mg in the weight management trial, the prevalence of metabolic syndrome was reduced (25.6% at week 28 *vs* 50.0% at baseline)^[58]. Normalization of elevated baseline ALT occurred in 25%-46% of patients in the weight management trial in a dose dependent manner (*vs* 18% in placebo group), while in the SUSTAIN-6 trial, reductions in ALT levels were recorded only at the 1.0 mg dose (9% *vs* placebo, $P = 0.0024$) at week 104^[58]. However, changes in ALT and hsCRP levels were not significant after adjustment for weight change. Histological data are awaited from an ongoing phase 2 trial of semaglutide in biopsy-proven NASH (NCT02970942)^[58] (Table 2).

CONCLUSION

Both animal and clinical studies are highly promising for the beneficial effect of GLP-1RAs in patients with NAFLD. Importantly, GLP-1RAs have good safety profile, since the most common adverse events are nausea and diarrhea, while the risk of pancreatitis is very small and not confirmed in a recent meta-analysis^[59]. Among GLP-1RAs, liraglutide has been studied more extensively in the setting of NAFLD, leading to amelioration in both hepatic and visceral fat accumulation as well as improvement in liver function tests and histological lesions in patients with NAFLD^[46,51]. Nonetheless, the need for daily injection is a major limitation, presumably affecting patients' medication compliance. Long-acting GLP1-RAs, such as dulaglutide and semaglutide, seem an appealing therapeutic option. Dulaglutide pharmacotherapy combines the beneficial effects of short-acting liraglutide on ameliorating anthropometric and laboratory parameters, such as body mass and ALT serum levels respectively, with the significant advantage of weekly injection administration^[42,60]. Beyond the latter advantage, disposable and prefilled devices for dulaglutide medication are also available^[60]. Regarding semaglutide, appears to have some

additional advantages to other GLP-1RA agents. Based on data from SUSTAIN-6, a placebo-controlled trial, semaglutide medication led to marked prevention of cardiovascular events, the predominant cause of mortality among NAFLD patients, while SUSTAIN-7 trial demonstrated the superiority of semaglutide over dulaglutide regarding glucose control and body weight reduction among T2DM patients^[61,62]. Of great interest, the recent Food and Drug Administration approval of oral semaglutide taken once a day for T2DM, might become the first-line approach for patients with both T2DM and NAFLD. Of note, a plethora of data concerning the efficacy of GLP-1RAs on NAFLD is based on exenatide. Indeed, exenatide exerts hepato-protective as well as glucose-lowering actions combined with remarkable amelioration of anthropometric parameters and liver dysfunction markers^[30,34]. However, similarly to liraglutide pharmacotherapy, the need for twice daily administration therapy appears as a significant limitation^[63]. On the other hand, pharmacotherapy with lisixenatide requires once daily administration and beyond that, its tolerability profile seems to be better than exenatide, since T2DM patients treated with lisixenatide experienced markedly less nausea than the corresponding exenatide treated group of T2DM patients^[64]. Nevertheless, more data with lisixenatide efficacy on NAFLD modification are required in order to consider the aforementioned drug as a propitious therapeutic opportunity. In conclusion, it seems that GLP-1RA administration in patients with T2DM is an attractive therapeutic option associated with weight loss, glycemic control and potentially reversal of biochemical and/or histological features of NAFLD in patients with concomitant NAFLD. However, larger, long-term, randomized, controlled trials should be conducted to better define the role of these agents in the management of NAFLD.

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